Homology modeling and deletion mutants of human nicotinamide mononucleotide adenylyltransferase isozyme 2: new insights on structure and function relationship.

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Public Summary:
Nicotinamide mononucleotide adenylyltransferase (NMNAT) catalyzes the formation of NAD by means of nucleophilic attack by 5'-phosphoryl of NMN on the alpha-phosphoryl group of ATP. Humans possess three NMNAT isozymes (NMNAT1, NMNAT2, and NMNAT3) that differ in size and sequence, gene expression pattern, subcellular localization, oligomeric state and catalytic properties. Of these, NMNAT2, the least abundant isozyme, is the only one whose much-needed crystal structure has not been solved as yet. To fill this gap, we used the crystal structures of human NMNAT1 and NMNAT3 as templates for homology-based structural modeling of NMNAT2, and the resulting raw structure was then refined by molecular dynamics simulations in a water box to obtain a model of the final folded structure. We investigated the importance of NMNAT2's central domain, which we postulated to be dispensable for catalytic activity, instead representing an isozyme-specific control domain within the overall architecture of NMNAT2. Indeed, we experimentally confirmed that removal of different-length fragments from this central domain did not compromise the enzyme's catalytic activity or the overall tridimensional structure of the active site.

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